

CLAIMS

1. A method of determining, particularly in situ, physical, chemical and/or biological properties or state variables, particularly substance concentrations, temperature, pH and/or physical fields, and/or the change in physical, chemical and/or biological properties or state variables in an examination area of an examination object by determining the change in the spatial distribution of magnetic particles in this examination area or in parts thereof as a function of the effect of, particularly physical, chemical and/or biological, influencing variables on at least a part-area and/or in the, particularly physical, chemical and/or biological, conditions in at least a part-area of the examination area, by means of the following steps:
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- 10 a) introducing magnetic particles into at least part of the examination area in a first state in which in the examination area or in parts thereof at least some of the magnetic particles that are to be examined are agglomerated and/or coupled to one another in pairs or more, particularly covalently, ionically, coordinatively or via hydrogen bridge bonds or Van der Waals bonds, in particular are at least partially restricted in terms of their freedom of movement, or introducing magnetic particles into at least part of the examination area in a
- 15 second state in which the particles are deagglomerated and/or decoupled and can be agglomerated and/or coupled,
- b) generating a magnetic field with a spatial profile of the magnetic field strength such that there is produced in the examination area a first part-area having a low magnetic field strength and a second part-area having a higher magnetic field strength,
- 20 c) changing the, in particular relative, spatial position of the two part-areas in the examination area or changing the magnetic field strength in the first part-area so that the magnetization of the particles is locally changed,
- d) detecting signals that depend on the magnetization in the examination area
- 25 that is influenced by this change, and
- e) evaluating the signals so as to obtain information about the change in the spatial distribution of the magnetic particles and/or about physical, chemical and/or biological state variables and/or the change therein in the examination area.
- 30 2. A method as claimed in claim 1, characterized in that at least those state variables in which magnetic particles pass from the first state pass to the second state are detected in an examination area, in particular by the relative arrangement of the magnetic

particles changing toward a deagglomeration and/or decoupling and/or by the individual magnetic particles assuming on average a greater distance from one another, or in which the magnetic particles pass from said second state to said first state.

- 5     3.             A method as claimed in claim 2, characterized in that the passing of the magnetic particles from the first state to the second state and/or from the second state to the first state takes place thermally, by means of radiation, acid, base, electrical or magnetic fields, ultrasound and/or enzymatically.
- 10    4.             A method as claimed in any of the preceding claims, characterized in that the change in the spatial distribution of the magnetic particles that is determined in the examination area is or can be correlated with a local concentration, temperature, pressure, viscosity and/or a local pH value.
- 15    5.             A method as claimed in any of the preceding claims, characterized in that according to a first state agglomerated and or coupled-together magnetic particles are in a spatially delimited, solid or viscous medium which can be physically, chemically and/or biologically modified, dissolved and/or degraded.
- 20    6.             A method as claimed in claim 5, characterized in that the medium comprises polysaccharides, starch, in particular dextrans or cyclodextrans, waxes, oils, fats or gels.
7.             A method as claimed in claim 5, characterized in that the medium comprises microorganisms, in particular bacteria.
- 25    8.             A method as claimed in any of the preceding claims, characterized in that the magnetic particles in the agglomerated or coupled-together state are located in the region of the surface of a particulate, in particular liquid or gaseous, medium.
- 30    9.             A method as claimed in any of the preceding claims, characterized in that the magnetic particles become saturated upon application of an external magnetic field, in particular having a strength of about 100 mT or less.

10. A method as claimed in any of the preceding claims, characterized in that the magnetic particle is a multidomain or monodomain particle the magnetization of which can be reversed by means of Neel's rotation and/or by means of Brown's rotation.

5 11. A method as claimed in any of the preceding claims, characterized in that the magnetic particle is a hard- or soft-magnetic multidomain particle.

12. A method as claimed in any of the preceding claims, characterized in that the magnetic particle is a monodomain particle the magnetization of which is reversed by Neel's  
10 and Brown's rotation, or a soft-magnetic multidomain particle of asymmetric shape.

13. A method as claimed in any of the preceding claims, characterized in that first magnetic particles, bound to at least one functional binding unit, in particular a functional group, a DNA sequence, an RNA sequence and/or an aptamer, and at least second magnetic  
15 particles, bound to at least one functional binding unit, in particular a functional group, a DNA sequence, an RNA sequence and/or an aptamer, are present in and/or introduced into the examination area and in that there is present in and/or is introduced into the examination area at least one compound which has at least a first functional binding unit, in particular a functional group, a complementary DNA sequence, a complementary RNA sequence and/or  
20 a complementary aptamer sequence, that interacts in a binding manner with at least one functional binding unit of the first magnetic particles and which has at least a second functional binding unit, in particular a functional group, a complementary DNA sequence, a complementary RNA sequence and/or a complementary aptamer sequence, that interacts in a binding manner with at least one functional binding unit of the second magnetic particles.

25 14. A method as claimed in any of the preceding claims, characterized in that the evaluation takes place by means of the following steps:

a) selection of a path for the movement of the first part-area having a low magnetic field strength within the examination area,

30 b) recording of reference data by means of reference samples along the path according to a) at at least one location, in particular a number of locations, in the case of at least two, in particular a number of, external parameters using at least a first receiving coil,

c) interpolation and/or extrapolation of the reference data recorded in b) in respect of points and external parameters not recorded in step b),

- d) measurement of the path within the examination area in a sequence that is identical or substantially identical to that used for the recording of data by means of reference samples according to b) via at least a first and/or second receiving coil, and
- e) comparison of the data obtained according to d) with the reference data
- 5 according to b) and/or c), in particular by means of error square minimization.

15. A method as claimed in claim 14, characterized in that in a step c') that follows step c), the reference data obtained in steps b) and/or c) are converted to the characteristics of at least a second receiving coil used for the measurement in step d).

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16. A method as claimed in claim 14 or 15, characterized in that in a further step f) the data obtained by means of comparison in step e) are assigned to a gray value for a pixel to give an image, with the relative pixel intensity representing the degree of the determined external parameters.

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17. A method as claimed in claim 16, characterized in that in a further step g) the images obtained in step f) are displayed in a merged image.

18. A method as claimed in any of claims 14 to 17, characterized in that the

20 sequence of steps c') to g) or d) to g) is carried out at least twice, in particular a number of times.

19. A method as claimed in any of claims 14 to 18, characterized in that the part-area having a low magnetic field strength is moved by actuating and/or moving the coil

25 arrangement or in that in the case of a stationary part-area having a low magnetic field strength the examination object is moved or in that the examination object and the part-area having a low magnetic field strength are moved relative to one another at the same time.

20. The use of monodomain particles the magnetization of which is reversed by

30 means of Neel's and Brown's rotation and/or of soft-magnetic multidomain particles of asymmetric shape for viscosity measurements, in particular according to a method as claimed in claims 1 to 19.

21. Magnetic gas bubble composition, comprising one or more gas bubbles in a liquid medium wherein magnetic particles are present at the interface of the gas bubble and the liquid medium.
- 5 22. Magnetic gas bubble composition according to claim 21, further comprising a surfactant for localising the magnetic particles substantially at the interface between the gas bubble and the liquid medium.
23. Magnetic gas bubble composition according to claim 22, wherein the  
10 magnetic particles are attached to a surfactant molecule.
24. Magnetic gas bubble composition according to claims 21 to 23, wherein the diameter of the gas bubble is between one and 10  $\mu$ meters.
- 15 25. Magnetic gas bubble composition according to claims 21 to 24, wherein the bubble comprises a drug.
26. Magnetic gas bubble composition according to any one of claims 21 to 25, wherein the gas has a low water solubility, in particular wherein the gas does not  
20 substantially dissolve and/or does not rapidly dissolve in water, preferably a perfluorated gas.
27. Magnetic gas bubble composition according to any one of claims 21 to 26, wherein the average particle to particle distance between the magnetic particles at the interface between the gas bubble and the liquid medium is less than 10 times the magnetic  
25 particle size.
28. Magnetic gas bubble composition according to any one of claims 21 to 27, wherein the magnetic particles are monodomain particles having an anisotropy.
- 30 29. Magnetic gas bubble precursor for the manufacture of a magnetic gas bubble composition according to any one of claims 1 to 28, wherein the gas bubble precursor comprises a shell encompassing a gas volume and wherein the shell comprises magnetic particles.

30. Magnetic gas bubble precursor according to claim 29 , wherein the shell comprises a material that dissolves or reduces viscosity in contact with a liquid medium such that the magnetic particles gain freedom for movement when dispersed in the liquid medium.

5 31. Use of a magnetic gas bubble composition according to any one of claims 21 to 28 or a magnetic gas bubble precursor according to claims 29 or 30 as an imaging agent in a magnetic particle imaging technique, in particular for imaging pressure in an examination area by said technique, more particular for imaging elastic properties of the examination area by acoustic waves.

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32. Kit of magnetic particle compositions comprising a first magnetic particle composition, a second magnetic particle composition and a third compound, wherein in the first magnetic particle composition the first magnetic particles are bound to at least one functional binding unit, in particular a functional group, a DNA sequence, an RNA sequence and/or an aptamer, wherein in the second particle composition the second magnetic particles are bound to at least one functional binding unit, in particular a functional group, a DNA sequence, an RNA sequence and/or an aptamer and wherein the third compound has at least a first functional binding unit, in particular a functional group, a complementary DNA sequence, a complementary RNA sequence and/or a complementary aptamer sequence, that interacts in a binding manner with at least one functional binding unit of the first magnetic particles and which has at least a second functional binding unit, in particular a functional group, a complementary DNA sequence, a complementary RNA sequence and/or a complementary aptamer sequence, that interacts in a binding manner with at least one functional binding unit of the second magnetic particles and wherein the average particle to particle distance in a state wherein the first and second magnetic particle bind with the third compound is such that the first and second magnetic particles are coupled in a first agglomerated state, preferably having a distance between the magnetic particles between 3 and 10 times the magnetic particle size.

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30 33. Functionalised magnetic particle composition comprising two or more magnetic particles that are according to a first state agglomerated and/or coupled-together in a spatially delimited way by a bond and/or by embedding in a solid or viscous medium which bond or embedding medium can be physically, chemically and/or biologically modified, dissolved and/or degraded to a second state of reduced agglomeration and wherein the

average particle to particle distance between the magnetic particles is less than 10 times the average magnetic particle size.

34. Functionalised magnetic particle composition according to claim 33, wherein  
5 the two or more magnetic particles are coated with a shell material that is does not quickly dissolve or degrade and are agglomerated and kept together with a bond that can be physically, chemically and/or biologically modified, dissolved and/or degraded to a second state of reduced agglomeration.

10 35. Functionalised magnetic particle composition according to claim 33 comprising coated particles comprising two or more magnetic particles wherein the average particle to particle distance between the magnetic particles is between 3 and 10 times the magnetic particle size and which particles are in a first state agglomerated and/or coupled-together in a spatially delimited way by a bond or embedded by a solid or viscous coating  
15 material which can be physically, chemically and/or biologically modified, dissolved and/or degraded.

36. Functionalised magnetic particle composition according to claim 35, wherein  
the magnetic particles are coated with a coating material that swells or shrinks to an extent  
20 depending on the conditions in the examination area, thereby changing the distance between the magnetic particles.

37. Functionalised magnetic particle composition according to claim 36, wherein  
the extent of swelling of the coating material depends on the ion strength of the aqueous  
25 medium in the examination area, in particular body fluids.

38. Magnetic particle composition having a magnetization curve having a step  
change, the step change being characterized in that the magnetization change, as measured in  
an aqueous suspension, in a first field strength window of magnitude delta around the  
30 inflection point of said step change is at least a factor 3 higher than the magnetization change in the field strength windows of magnitude delta below or in the field strength windows of magnitude delta above the first field strength window, wherein delta is less than 2000 microtesla and wherein the time in which the magnetisation step change is completed in the first delta window is less than 0.01 seconds.

39. Use of a magnetic particle composition according to claim 38 in any one of claims 1 to 37 .

- 5 40. An apparatus to determine the spatial distribution of magnetic particle and/or in situ, physical, chemical and/or biological properties or state variables, particularly substance concentrations, temperature, pH and/or physical fields, and/or the change in physical, chemical and/or biological properties or state variables in an examination area of an examination object comprising:
- 10 a) means to generate a magnetic field with a spatial distribution of the magnetic field strength such that the area of examination consists of a first sub-area with lower magnetic field strength and a second sub-area with a higher magnetic field strength,
- b) means to change the spatial location of both sub-areas in the area of examination so that the magnetization of the particles changes locally,
- 15 c) means for the acquisition of signals that depend on the magnetization in the area of examination influenced by this change,
- d) means for the evaluation of said signals to obtain information about the spatial distribution of the signals in the area of examination and
- e) means to perform calibration measurements as in method claims 14 to 19,
- 20 comprising means to record reference data on reference samples and means to compare the signals obtained in step c and/or d with the reference data to evaluate spatially resolved information about in situ, physical, chemical and/or biological properties or state variables in the area of examination.

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